REMARKS/ARGUMENTS

I. Amendments to the specification

Four paragraphs were amended to correct typographical errors. The amendments do not introduce new matter. Entry of these amendments is respectfully requested.

II. Status of the claims

Claim 1 was amended because the term "non-denatured protein" has antecedent basis in the preamble.

Claim 11 was amended to correct a typographical error and because the term "extraction surface" has no antecedent basis.

Claim 14 was amended to correct the fact that the term "multi-protein complex" has antecedent basis in the preamble. Claim 14 was further amended to describe the multi-protein complex as being comprised of **at least** a first protein and a second protein. Support for the amendment can be found in Applicant's specification on page 57, lines 12 - 14.

The amendments do not introduce new matter. Entry of these amendments is respectfully requested.

III. Priority

On page 2 of the Office action, the Examiner states that claims 14 – 40 are not sufficiently supported by application nos. 10/434,713 and 60/523,518. Applicants acknowledge the Examiner's assertion.

IV. Claim rejections under 35 U.S.C. § 102

Before addressing the individual rejections, Applicants would like to point out some of the ways in which the devices and methods of the instant invention differ from those in Laursen ("Laursen", US 6,274,371) and Hagen et al. ("Hagen", US 4,810,381), cited by the Examiner.

A. Description of the instant invention

The extraction channels of the instant invention are **open** channels. The extraction channels do not contain a packed bed of media. Instead, the **extraction media is attached to the inner surface** of the extraction channel. Since the channels are **open** and because of the placement of the solid phase **extraction surface on the inner surface** of the extraction channels, the methods of the instant invention are fundamentally different from the methods taught by Laursen and Hagen and thus, cannot be anticipated by the cited references.

Because the channels of the instant invention are open and do not contain a packed bed of medium, the flow characteristics differ dramatically from the flow characteristics of a conventional chromatography column such as the one taught by Laursen. According to the extraction methods of the claimed invention, a sample containing an analyte of interest (native protein, a non-denatured protein or a multi-protein complex) is introduced into the channel as a flowing stream. As the stream moves through the channel, the analyte is captured by the extraction surface, which is adjacent or parallel to the flowing stream. The flow in the capillary channel is likely to be parabolic with the velocity of the flow fastest at the center of the channel. The velocity of the stream decreases toward the channel wall until flow velocity is near zero at the wall.

In the chromatography column taught by Laursen, the sample flow path is perpendicular to the bed of medium. The sample passes directly though the beads in the bed of medium hitting the beads head on and then flowing around the beads. Each bead has multiple analyte binding sites and the beads are in intimate contact with each other. Therefore, in the Laursen's column, the analyte binding sites are much closer together than in the open channels of the instant invention.

Additionally, since the channels of the claimed invention are open and do not contain a packed bed of medium, there are a number of differences in their methods of use. For example, claims 15, 16, 35, 36, 38 and 39 recite a method for purging the channel with a gas to remove bulk liquid between the adsorption and desorption steps.

In contrast, it wouldn't work to purge Laursen's column with a gas between the adsorption and elution steps. Introduction of air into the packed bed would disrupt the flow characteristics of the bed such that the desorption solution would not flow through the entire bed, making the elution step very inefficient.

Another method used with extraction channels of the instant invention is back and forth (bi-directional) flow.[1] Pumping the sample solution back and forth through the channel can promote more efficient adsorption of the analyte to the extraction surface. Pumping a small volume of desorption solution back and forth through the channel can facilitate recovery of highly concentrated analyte.

The columns taught by Laursen are not capable of back and forth flow. To recover the protein from Laursen's column, an elution solution is pumped through the column, fractions are collected and the MBL fraction is recovered.

B. Laursen

In section 3 on page 3 of the Office action, the Examiner rejected claims 1-11, and 14-17 as allegedly anticipated by Laursen. Applicants respectfully traverse the rejection. In order for a reference to be deemed anticipatory, it must disclose each element of the claimed invention. Laursen fails to do this. Based on the definitions of the claim terms in Applicant's specification, Laursen fails to disclose adsorbing a non-denatured protein to the **extraction surface** of an **extraction channel**.

Laursen teaches the use of conventional affinity chromatography for the purification of a particular protein, mannan-binding lectin (MBL). Laursen uses a packed bed of medium in a chromatography column. In column 3, line 56 through column 4, line 16, Laursen discusses properties of desirable matrices (media) and lists a number of preferred materials. In Example 1, Laursen teaches a column packed with 10 liters of Sepharose CL4B.

In contrast to the teachings of Larsen, the methods of the instant invention do not utilize a packed bed of medium in a chromatography column. Instead, the extraction channels of the instant invention are **open** channels that can be comprised of **tubing** such as fused silica capillary tubing. In Applicant's specification, the extraction channels are defined as follows.

> The term "channel" encompasses but is not limited to the various forms of conventional capillary **tubing** that are used for applications such as chromatography and capillary electrophoresis, e.g., fused silica capillary tubing. Thus, the term also encompasses other **open** channels of similar dimensions, having one or more capillary flow passageways, each having an inlet and outlet. Examples include a capillary tube, a bundle of

[1] Applicant's specification, page 4, lines 12 – 18.

> tubes, a solid block or chip having one or more passageways or flow cells running therethrough, e.g., a microfluidics device such as those associated with BiaCore, Inc. (Piscataway, NJ), Gyros, Inc. (Uppsala, Sweden), Caliper Technologies, Inc. (Mountain View, CA) and the like.[2]

The instant invention is further distinguished from Laursen by the position of the extraction surface on the inner surface of the open channel. The position of the extraction surface is described in Applicant's specification as follows.

> In preferred embodiments, the extraction surface covers the entire **inner periphery** of the extraction channel, as opposed to on just one face of the channel.[3]
>
> Fig. 1 shows a tubular channel 2, the inner surface of which is coated with a solid phase extraction medium 4.[4]

Independent claim 1 is drawn to a method of extracting a non-denatured protein comprising adsorbing the non-denatured protein to the **extraction surface** of an **extraction channel**. As noted above, Applicant's specification describes the term **extraction channel** as an **open** channel and describes the location of the **extraction surface on the inner periphery** of the extraction channel. The Examiner alleges "Laursen teaches a process for extracting a non-denatured protein comprising adsorbing a non-denatured protein to the extraction surface of an extraction channel..." But Laursen does not teach methods to capture an active protein using an **open** extraction channel. Laursen uses a conventional affinity chromatography column with a packed of medium. Laursen does not teach an **extraction surface on the inner periphery** of a channel. Laursen's extraction surface is the packed bed of chromatography medium. Therefore claim 1 is not anticipated by Laursen. Since claims 2 - 10 depend from claim 1 and thus, contain the same limitations, and further limit claim 1, claims 2 - 10 are not anticipated by Laursen.

Similarly, claim 11 is drawn to a method of preparing a native protein comprising adsorbing a protein to the **extraction surface** of an **extraction channel**. Claim 14 is drawn to a method for extracting a multi-protein complex comprising introducing the multi-protein complex to

[2] Applicant's specification, page 24, lines 5 – 13.
[3] Applicant's specification, page 8, lines 14 – 15.
[4] Applicant's specification, page 19, lines 26 – 27.

an **extraction channel** whereby the multi-protein complex is adsorbed to the **extraction surface**. Since the extraction channel recited in claims 11 and 14 is described in Applicant's specification as an **open channel**, and since the extraction surface recited in claims 11 and 14 is described in Applicant's specification as covering the **inner periphery of the channel**, claims 11 and 14 are not anticipated by Laursen. Since claims 15 – 17 depend from claim 14 and thus, contain the same limitations, and further limit claim 14, claims 15 – 17 are not anticipated by Laursen.

On page 3 of the Office action the Examiner alleges "The MBL sample solution comprises a multi-protein complex comprising at least a first and second protein and the extraction surface binds the multi-protein complex and the multi-protein complex is adsorbed to the extraction surface." The Examiner cites column 3, lines 14 – 17 and column 11, lines 48 - 51. Applicants respectfully disagree. In column 3, lines 14 – 17, Laursen describes the MBL containing solution as a "complex protein mixture". A complex protein mixture is a mixture of proteins, which is significantly different from a protein complex. Nowhere does Laursen say that MBL is a protein complex. Protein complexes are two or more proteins held together by mutually attractive chemical forces while MBL is a single protein within a protein mixture.

> The Examiner further describes Laursen's teachings as follows:
> The eluted non-denatured protein is used in a process that requires that the protein be non-denatured for the process to be successful. The process is an analytical method that is an activity assay, and ELISA-type assay. The method does not involve the introduction of joule heating to the non-denatured protein. The extraction is performed at a temperature in the range of 0 to 25 degrees Celsius. The eluted protein retains its function and is in its native state. A wash solution is passed through the channel before a first desorption solution is passed through the channel.

Applicants argue that these allegations are moot since Laursen's method involves conventional affinity chromatography while claims 1-11 and 14-17 are drawn to **open** solid phase extraction **channels** having an **extraction surface on the inner periphery** of the channel. In view of the foregoing, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 102.

C. Hagen et al.

In section 4 on page 4 of the Office action, the Examiner rejected claims 14 - 40 as allegedly anticipated by Hagen.

Applicants respectfully traverse the rejection on the basis that Hagen does not teach all the elements of claims 14 - 40. Particularly, Hagen does not teach extraction using an **open channel** having the **extraction surface on the inner periphery** of the channel. Additionally Hagen does not teach methods for extracting multi-protein complexes.

The Examiner describes Hagen as "teaching a method of introducing a sample solution containing three separate proteins into a column and eluting each protein with a separate solution." However, Hagen does not even teach the use of a column or a channel. In fact, Hagen never uses the term "channel" to describe their invention. Instead, Hagen teaches a composite chromatographic article and methods of use. In one embodiment, Hagen's chromatographic article is a sheet and the sample is introduced into the sheet at an angle of 90 degrees to the surface of the sheet.[5] In a second embodiment, the chromatographic article is a disk or a strip. In this embodiment (which is analogous to thin layer or paper chromatography), the sample moves through the chromatographic article by capillary action in a direction parallel to the article surface.[6]

Claims 14 – 40 are drawn to solid phase extraction methods for extracting multi-protein complexes. Multi-protein complexes are defined in Applicant's specification as "a complex of two or more proteins held together by mutually attractive chemical forces, typically non-covalent interactions".[7] Hagen does not teach methods for purifying multi-protein complexes. In the passage cited by the Examiner, Hagen describes the separation of three different horse proteins, hemoglobin, myoglobin and cytochrome C using a three-step desorption process.[8] These are individual proteins, not components of a multi-protein complex.

Finally, the Examiner alleges, "Between solutions, the channel is purged so that the extraction channel is substantially free of bulk liquid." But Hagen does not use a channel or a purge step. Hagen does not contain the term "channel" or the term "purge".

Independent claims 14 and 29 are drawn to methods for extracting multi-protein complexes using an extraction channel comprising an extraction surface. Since Hagen is not using an extraction channel and since Hagen does not teach a method for extracting multi-protein complexes, claims 14 and 29 are not anticipated by Hagen. Since claims 15 – 28 depend from claim 14, and thus

[5] Hagen, column 8, lines 36 -38.
[6] Hagen, column 8, lines 62 -66 and column 9, lines 3 - 6.
[7] Applicant's specification, page 57, lines 12 – 14.
[8] Hagen, column 10, line 60 through column 11, line 24.

contain the same limitations, and further limit claim 14, claims 15 – 28 are not anticipated by Hagen. Similarly, since claims 30 – 40 depend from claim 29, and thus contain the same limitations, and further limit claim 29, claims 30 – 40 are not anticipated by Hagen. In view of the foregoing, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 102.

CONCLUSION

The Commissioner is hereby authorized to charge $230 for a two-month extension of time to Deposit Account No. 50-2852. In the event that an extension of time is required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely. The Commissioner is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. 50-2852.

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (408)267-7214.

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